REMARKS

IN THE CLAIMS

Applicants respectfully acknowledge the Examiner's entrance of the claim amendments proposed in Applicants' response dated December 19, 2007. Applicants also gratefully acknowledge the Examiner's indication in the Advisory Action dated January 29, 2008, that the Applicants' response has overcome the rejection of Claim 1, and dependent claims 2-12, 14, 16 and 18-23 under 35 USC 112, second paragraph.

New Amendments

The independent Claims 1 and 24 have been amended to point out with greater clarity and particularity the subject matter regarded by Applicants as their invention, to specify that the subject tissue recited in the preamble, that is, "which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis . . ." (Claim 1), or "a tissue in which 40% or more of the cells normally express MN/CA IX protein, but said tissue loses MN/CA IX expression or expression of MN/CA IX is significantly reduced upon carcinogenesis . . ." (Claim 24), is "selected from the group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic

epithelium and rete ovari, basal cells of hair follicles, and central nervous system choroid plexus." Applicants respectfully point out that the amendments to Claims 1 and 24 are supported in the instant application, at the least by original Claim 3, now canceled.

The number and types of species comprised within the subject genus of preneoplastic/neoplastic diseases are described in the instant Specification at least at page 5, lines 11-18; at page 9, lines 3-21; at page 22, line 30 to page 23, line 7; at page 23, line 30 to page 24, line 31; and at page 45, line 31 to page 46, line 3 (original Claim 3). For example, exemplary species can be found at page 5, lines 11-15 of the Specification, which reads:

> Said tissue is preferably selected from the group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic epithelium and rete ovarii, basal cells of hair follicles, and central nervous system choroid plexus.

In addition, original claim 3 [at page 45, line 31 to page 46, line 3], which is now canceled, recites the same exemplary tissues that are subject to the methods of the invention.

Applicants respectfully submit that no new matter has been entered by the above amendments to the pending claims, and

respectfully request entry of the above amendments and reconsideration of the application as amended.

I. **35 USC 112, First Paragraph Rejection - Written Description**

Claims 1-11, 14, 16 and 18-24 stand rejected under 35 USC 112, first paragraph, as "failing to comply with the written description requirement . . ." [Final Office Action dated October 19, 2007, at page 5]. The Final Office Action further states that "[t]he specification does not disclose and the prior art does not teach the genera of tissue samples taken from a subject vertebrate with a disease that affects a tissue which normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis . . ." [Final Office Action, middle of page 5].

Applicants respectfully submit that the amendments to independent Claims 1 and 24 overcome the instant rejection. Applicants respectfully point out that Claim 3 has been canceled and independent Claims 1 and 24 have been amended, to specify that "the genera of tissue samples taken from a subject vertebrate with a disease that affects a tissue which normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis" is "selected from the group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including

ductular efferens and rete testis, ovary including surface coelomic epithelium and rete ovari, basal cells of hair follicles, and central nervous system choroid plexus."

Applicants respectfully submit that the genus of tissue samples subject to the claimed methods in the claims as amended is clearly defined and supported in the instant specification. Applicants further argue as in their previous responses dated 8/16/07 and 12/19/07 that "there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." [MPEP § 2163.]

The Advisory Action at page 2 admits that "Ivanov et al. [Am. J. Path., 158(3): 905-919 (2001)] provides a limited number of species encompassed by the genus . . ." but also states that

> [t]he examiner disagrees with the argument that one of skill in the art would reasonably expect normal tissues with high expression of CA IX (in addition to gastric mucosa, gallbladder, and bilary [sic] epithelium), primarily normal tissue with high rates of proliferation, would be expected to lose CA IX expression upon carcinogenesis. Such a trend is not demonstrated by the prior art or the specification.

[Advisory Action, middle of page 2.] Applicants respectfully point out that, contrary to the Examiner's understanding of the written description requirement, "[a]n applicant shows possession of the claimed invention by describing the claimed

invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." [MPEP § 2163.] Also, "[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed . . . ," and "**rejection of an original claim for lack of written description should be rare**." [MPEP § 2163; emphasis added.]

Further, the exemplary species within the recited genus of diseases are adequately described in the instant Specification, at the least at page 5, lines 11-18; at page 9, lines 3-21; at page 22, line 30 to page 23, line 7; at page 23, line 30 to page 24, line 31; and at page 45, line 31 to page 46, line 3 (original Claim 3). Applicants respectfully remind the Examiner that for sufficient written description, it is not required that they establish that all the recited tissues that normally express MN/CA IX lose expression upon carcinogenesis.

Even so, Applicants respectfully contend that the trend had already been established in Ivanov et al. specifically for those tissues identified in the specification and amended Claims 1 and 24, for tissues other than "gastric mucosa, gallbladder, and biliary epithelium" as stated by the Examiner. Applicants respectfully remind the Examiner that Applicants previously pointed out the support in Ivanov et al. for the

claimed genus of preneoplastic/neoplastic tissues that lose MN/CA IX expression upon carcinogenesis, particularly at page 909 and in Tables 3 and 4 [Ivanov et al., at pages 911 and 913]. Based on data from Tables 3 and 4, Applicants provide a summary chart below comparing CA IX expression in normal and tumor tissues, for those tissues in which CA IX is normally expressed.

Data based on Tables 3 & 4 of Ivanov 2001

Tissue	Normal CA IX Expression	Corresponding Tumor	CA IX Tumor Expression (% cases diffuse)
Gastric fundus	diffuse	Carcinoma of stomach/duodenum	0%
Ductal cells of duodenum	diffuse		
Crypt cells of duodenum	diffuse		
Gallbladder/biliary tract	diffuse	Pancreas/gallbladder adenocarcinoma	30%
testis	diffuse	Germ cell[1]	0%
ovary	diffuse	Epithelial carcinoma, Cystadenoma of LMP, sex-cord tumor	0-67%
Basal hair follicle skin cells	diffuse	Squamous/basal cell carcinoma	50%
Choroid plexus	diffuse	Choroid plexus tumor	0%

Applicants respectfully point out that according to the above Ivanov et al. data, for many of those tissues in which CA IX is normally expressed in a "diffuse" manner,[2] in the corresponding

1. Unknown if "germ cell" is derived from ovary, testis or both.

2. "Diffuse, ≥ 40% of cells within a field stain positively." [Ivanov et al., footnote on page 911.]

tumors CA IX expression was "diffuse" in none (0%) of the cases. For the remaining tissues, CA IX expression was diffuse in 30%-67% of the cases, rather than in 100% of the cases, and therefore, CA IX expression was presumably significantly decreased in those tissues. Therefore, Applicants respectfully conclude that the Examiner is incorrect in stating that "[s]uch a trend [of loss of CA IX expression upon carcinogenesis] is not demonstrated by the prior art or the specification."

Case Law Cited

At page 2 of the Advisory Action, the Examiner reapplies University of California v. Eli Lilly and Co., 43 USPQ2d 1398 at 1406 (Fed. Cir. 1997), stating that "the genus lacking written description in the instant case is a genus of tissue samples from a disease that affects a tissue which normally expresses MN/CA IX protein but loses or has significantly reduced MN/CA IX expression upon carcinogenesis." Applicants respectfully point out that the Lilly case cited by the Examiner is not relevant to the claims as amended. According to the claims as amended, the specific diseases comprised within the genus are finite and not unknown, unlike the sequence of human insulin gene in Eli Lilly.

Conclusion

Applicants respectfully request that the Examiner reconsider the instant rejection in view of the amendments to the independent Claims 1 and 24 for particularity and clarity and the above remarks, and withdraw the instant 35 USC § 112, first paragraph written description rejection.

II. 35 USC 112, First Paragraph (Enablement)

Claims 1-11, 14, 16 and 18-24 stand rejected under 35 USC 112, first paragraph, as "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims." [Final Office Action, at page 10.] More specifically, the Examiner argues that the specification

> [w]hile being enabling for a method of predicting survival of a patient with gastric cancer . . . does not reasonably provide enablement for a method which is prognostic for every preneoplastic/ neoplastic disease afflicting a subject vertebrate, wherein said disease affects a tissue, which tissue normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis, comprising . . . (d) determining that said subject vertebrate has every type of poorer prognosis. . . .

[Final Office Action, ¶ bridging pages 9-10; emphasis in the original.]

The Examiner further states at page 3 of the Advisory Action dated 1/29/08 that "[i]n regards to the argument that the number of preneoplastic/neoplastic diseases to which the claimed methods apply is relatively small, it is unclear which preneoplastic/neoplastic diseases are encompassed by the claimed methods (see written description rejection above) and it would require undue experimentation to identify said diseases."

Applicants respectfully submit that the amendments to the independent Claims 1 and 24 address the instant rejection. Applicants respectfully point out that Claim 3 has been canceled, and independent Claims 1 and 24 have been amended to point out with greater particularity and clarity each of the subject tissues "which normally expresses MN/CA IX protein, but loses or has significantly reduced MN/CA IX expression upon carcinogenesis" [preamble of Claim 1]; those tissues are "selected from the group consisting of gastric mucosa, gallbladder, biliary ducts, ductal cells of duodenal glands, testis including ductular efferens and rete testis, ovary including surface coelomic epithelium and rete ovari, basal cells of hair follicles, and central nervous system choroid plexus."

The independent Claims 1 and 24 have then been amended for greater particularity and clarity to list the particular tissues affected by preneoplastic/neoplastic disease which are

the subject of the claimed methods. Applicants respectfully submit that such a specific listing clarifies and particularizes the scope of the claims, and for reasons detailed in the Amendment (submitted to the PTO on 08/16/07) and the Amendment After Final (submitted to the PTO on 12/19/07), the subject matter of which Amendments is herein incorporated by reference, that there can be no doubt that the scope of enablement provided in the subject application bears at least a "reasonable correlation" to the scope of the claims. MPEP § 2164.08 states for example: "As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims."

MPEP 2164.08 goes on to state:

> How a teaching is set forth, by specific example or broad terminology, is not important. *In re Marzocchi*, 439 F.2d 220, 223-24 169 USPQ 367, 370 (CCPA 1971). . . . One does not look to the claims but to the specification to find out how to practice the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1558, 220 USPQ 303, 316-17 (Fed. Cir. 1983); *In re Johnson*, 558 F.2d 1008, 1017, 194 USPQ 187, 195 (CCPA 1977). In *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:
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> > [T]o provide effective incentives, claims must adequately protect inventors. **To demand that the**

> **first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.**

[Emphasis added.]

MPEP § 2164.08 further distinguishes Amgen Inc. v. Chugai Pharmaceutical Co. Ltd, 18 USPQ2d 1016 (Fed. Cir. 1991) in a manner analogous to that provided by the Applicants in the earlier Amendments, stating that as in the instant application:

> [W]hen claims are directed to any purified and isolated DNA sequence encoding a specifically named protein where the protein has a specifically identified sequence, a rejection of the claims as broader than the enabling disclosure is generally not appropriate because one skilled in the art could readily determine any one of the claimed embodiments.

Applicants respectfully clarify that as pointed out at the very beginning of the Manual of Patent Examining Procedure (MPEP) Section 2164 "The Enablement Requirement":

> **The invention that one skilled in the art must be enabled to make and use is that *defined by the claim(s)*** of the particular application or patent.
>
> . . . . [T]o comply with 35 U.S.C. 112, first paragraph, **it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment** absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l*

> *Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003). . . .

[Emphasis added.] In *CFMT, Inc. v. YieldUP International Corp.* (2003), *supra*, the Federal Circuit emphasized that a patent need only **enable** the claimed invention and need not meet a **commercial** standard not recited in the patent's claims. The Federal Circuit stated in that case [at 349 F.3d at 1338]:

> Enablement does not require an inventor to meet lofty standards for success in the **commercial** marketplace. Title 35 does not require that a patent disclosure **enable** one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.

[Emphasis in bold in the original; underlined emphasis added.]

As pointed out in MPEP § 2164 and as particularized in the above quotes, only what is "defined by the claim(s)" needs to be enabled. [MPEP § 2164.] The Examiner appears to be arguing that every type of prognosis needs to be enabled, for example, days to recurrence for a particular disease. But it is not every type of poorer prognosis and every end point that needs to be enabled for claims that are simply methods to determine whether a particular patient has a poorer prognosis when compared with other patients that have the same preneoplastic/neoplastic disease. How that poorer prognosis is defined, that is, as set forth in claim 10 as "measured in terms of shortened survival, increased risk of recurrence . . . , or

diminished or refractory responses to treatment, following treatment and/or surgical removal of the tumor . . ." does not mean that exact, commercial end points have to have been determined before the application is filed.

The lofty standard that is apparently being proposed as necessary by the Examiner, would mean that the methods would have to be perfected after years of accumulated clinical data, before filing to meet enablement requirements. Such a proposed standard would hardly be in tune with the purpose recited in the U.S. Constitution for granting patents, that is, "to promote the progress of science and the useful arts by securing for limited times to . . . inventors the exclusive right to their respective . . . discoveries." The case law is clear that pioneer inventions are entitled to broad claim coverage.[3] Applicants respectfully submit that the goal of the Constitution quoted above would not be served by refusing pioneer inventors claims to their new contribution to cancer prognosis.

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3. A basic patent on a pioneering invention is entitled to be interpreted broadly. Texas Instruments, Inc. v. United States ITC, 231 USPQ 3833 (Fed. Cir. 1986).

The Court of Customs and Patent Appeals (CCPA), predecessor court to the Federal Circuit,[4] stated in In re Goffe, 191 USPQ 429 at 431 (CCPA 1976):

> [T]o provide effective incentives, claims must adequately protect inventors. **To demand that the first to disclose shall limit his claims to what he has found will work. . . . would not serve the constitutional purpose of promoting progress in the useful arts.**

[Emphasis added.]

The CCPA further pointed out in In re Hogan and Banks, 194 USPQ 527 at 537 (CCPA 1977):

> As pioneers, . . . they would deserve broad claims to the broad concept. What were once referred to as 'basic inventions' have led to 'basic patents,' which amounted to **real incentives, not only to invention and its disclosure, but to its prompt, early disclosure. . . .**
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> **. . . To demand such restriction is merely to state a policy against broad protection for pioneer inventions, a policy both shortsighted and unsound from the standpoint of promoting progress in the useful arts, the constitutional purpose of the patent laws.**

[Emphasis added.]

In In re Fisher, 166 USPQ 28 at 24 (CCPA 1970), the CCPA considered it "apparent" that a pioneering invention should be able to dominate the future patentable inventions of others

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4. The holdings of the CCPA were adopted as precedent by the Federal Circuit in South Corp. v. United States, 215 USPQ 657 (Fed. Cir. 1982).

where those inventions were based in some way on his/her teachings, that is, where "the improvement was made possible by his work." *Previously, it was unknown whether MN/CA IX expression patterns in preneoplastic/neoplastic tissues, which tissues normally express MN/CA IX but lose expression upon carcinogenesis, could be used for prognosis. The recognition by the Applicants that MN/CA IX expression can be used for prognosis in those preneoplastic/neoplastic tissues that normally express MN/CA IX, but lose expression upon carcinogenesis, provides a benefit to the public as another option for cancer prognosis, and only relates to a limited number of tissues.*

Aspects of the Applicants' inventions are counter-intuitive at least at the time the inventions were made; that is, that a tissue that normally expresses MN/CA IX has absent or significantly reduced expression of MN/CA IX upon carcinogenesis, was found to have higher than average MN/CA IX expression in patients with poorer prognoses. Once one of skill in the art understands that discovery, routine testing methods using appropriate samples from a patient's tumor/metastic lesion and/or from tissues adjacent thereto can be compared to "comparable samples" (not just "any" samples) from patients with the same preneoplastic/neoplastic disease. That aspect is claimed in Claims 1-23.

Similarly counterintuitive is another aspect of the Applicants' inventions, that is, that if the level of MN/CA IX expression in samples taken from the invasion front of a tissue afflicted with a preneoplastic/ neoplastic disease (again not just "any sample") is compared to the level of MN/CA IX normally expressed in comparable samples of the same tissue unaffected by disease, that if the invasion front MN/CA IX expression is <u>not</u> absent nor at a significantly reduced level from that of the level in the unaffected tissue, that the patient has a poorer prognosis then if the invasion front MN/CA IX expression were absent or at a significantly reduced level in comparison to the tissue's normal MN/CA IX expression. That aspect is claimed in Claim 24.

Once one of skill in the art is privy to the counterintuitive aspects of the instant inventions, routine methods of detecting the level of MN/CA IX expression and of selecting appropriate samples and comparable samples can be used.

> **A patent need not teach, and preferably omits, what is well known in the art.** *In re Buchner*, . . . 18 USPQ2d 1331, 1332 (Fe. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, . . . 231 USPQ 81, 94 (Fed. Cir. 1986). . . .

[MPEP § 2164.01 "Test of Enablement" at page 2100-2194; emphasis in bold added.]

The instant application teaches a number of methods of how to make the comparison of MN/CA IX expression levels in, for example, a patient's tissue sample and in a comparable tissue sample, or, for example, in an invasion front tissue sample, and in a comparable normal sample. For example, a particular immunohistochemical staining method is at least outlined in original claim 8. **"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.** *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." [MPEP § 2164.01(b), 1st ¶; emphasis added.]

The first Office Action (mailed from the PTO on 05/17/07) cites Tockman et al. as teaching that "prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the **marker predictive value must be confirmed in prospective population trials**. . . ." [Office Action (05/17/07), pages 14-15.] For whatever Tockman et al. is being cited, Applicants respectfully submit that Tockman et al. cannot be cited as having any relevance to the standard for enablement under U.S. patent case law. Certainly no such "population trials" are required to validate disease end points, nor are the

establishment of any "disease end points" necessary for enablement under U.S. patent law.

It is only the claimed invention that requires enablement. The instant claims are only directed to determining whether a patient/vertebrate has a "poorer prognosis" or not in comparison to other patients/vertebrates with the same preneoplastic/neoplastic disease.

Tockman et al. does not raise the required "reason to doubt" of In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) to challenge the **presumptively enabling disclosure** of the instant application. As explained in the earlier Amendments, the cited portions of Tockman et al. relate only to diagnostic methods not generalized prognostic methods as claimed, and MN/CA IX has already been well established as a diagnostic marker. [See, for example, Robertson et al., Cancer Res., 64(17): 6160-6165 (2004) (of record).] Other differences between the instantly claimed inventions and Tockman et al. have been detailed carefully in the earlier Amendments, upon which the Applicants rely.

Tockman et al. has relevance in a clinical, commercial context, not in a patent case law enablement context. Whether under detailed analysis or in generalized concept, Tockman et al. has minimal, if any, significance in challenging the **presemptively enabling disclosure** of the instant invention.

The Federal Circuit quoted from In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) in In re Brana, 34 USPQ2d 1437 at 1441 (Fed. Cir. 1995) as follows:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

[Emphasis in the original.]

MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, supra; italicized emphasis in the original; underlined emphasis added.] Applicants respectfully submit that there is no reason to doubt the objective truth of statements relied upon for enabling support in the Specification for the claimed invention.

However, as pointed out in the earlier Amendments, even if hypothetically, the initial burden of proof had been shifted to the Applicants, the Applicants have shown in the earlier Amendments that that hypothetical burden would have been removed. The case for the hypothetical burden of proof not being shifted to the Applicants is even stronger in view of the above claim amendments that cite with particularity and clarity the particular group of preneoplastic/neoplastic tissues to which the claimed methods apply. There should be even less reason to doubt statements in the Specification relied upon for enabling support. Such a listing addresses any possible question of "undue experimentation" in regard to determining which tissues normally express MN/CA IX but lose or have significantly reduced MN/CA IX expression upon carcinogenesis, as raised in the 05/17/07 Office Action (bottom of page 15).

Applicants further respectfully argue as in the earlier Amendments (dated 8/16/07 and 12/19/07), that as the number of preneoplastic/neoplastic diseases to which the claimed methods apply is finite and clearly identified, it would require only routine experimentation to confirm the pattern of prognosis for diseases other than gastric cancer. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ

1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Finally, Applicants will demonstrate below that the state of the art substantiates the predictability of MN/CA IX as a biomarker for several different types of poorer prognosis, once the initial pattern has been established for a group of diseases associated with a particular MN/CA IX expression pattern.

Below the Applicants respectfully make points that show with more detail and evidence, that even if the citation of Tockman et al. could have hypothetically shifted the burden to the Applicants by challenging the Applicants' **presumptively enabling disclosure**, that such a hypothetical burden would have been dispelled and would have been shifted back to the Examiner.

Predictability of Prognosis Using CA IX

At page 3, the Advisory Action argues that "each of said type of prognosis [i.e., survival, risk of recurrence, and response to treatment] represent a particular type of disease state." Also, the Advisory Action cites Tockman et al. as evidence that "the state of the art for using expression of a particular marker as an indication of a particular diseased state is unpredictable," and as teaching that "prior to

successful application of newly described markers, research must validate said markers against known disease end points."

The Examiner goes on to state at page 3 of the Advisory Action:

> In regards to the argument that once a pattern of prognosis for a genus of diseases is established, it is conventional to apply that pattern for those diseases in the absence of evidence to the contrary, Tockman et al and Pastrokevo [sic] and Zavada provide evidence why one would not predict a single pattern of prognosis for the genus of diseases encompassed by the claimed methods.

Applicants respectfully disagree. As taught by MPEP § 2164.03 "Relationship of Predictability of the Art and the Enablement Requirement [R-2]":

> The "predictability of lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that clamed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. . . .
>
> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.

Applicants respectfully submit that what is known in the art of cancer prognosis confirms that MN/CA IX would be expected by those of skill in the art to be a highly predictable marker of multiple types of cancer prognosis, including "survival, risk of recurrence, and response to treatment." Because of its efficient induction by hypoxia (a universal attribute of solid tumors[5]) MN/CA IX is not **any** "particular marker" that is a subject of Tockman. For diseases of tissues in which MN/CA IX is not normally expressed, MN/CA IX has been established as a potential indicator of every type of poor prognosis, whether the disease end point is survival, risk of recurrence or response to treatment. Because of MN/CA IX's close association with tumor hypoxia and tumor aggressiveness, Applicants respectfully reiterate that one of skill in the art would expect that CA IX would correlate with several end points of prognosis.

Evidence of that point is provided in a 2006 review entitled, "Hypoxia: Importance in tumor biology, noninvasive measurement by imaging, and value of its measurement in the management of cancer therapy," prepared by The Cancer Imaging Program of the National Cancer Institute [Tatum et al., Int J

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5. "Hypoxia is a universal feature of solid tumors that arises as the tumor mass outgrows stromal vascular supply." [Abstract, Belozerov and Van Meir, Curr Opin Investig Drugs, 7(12): 1067-1076 (2006).]

Radiat Biol, 82(10): 699-757 (2006); copy enclosed], and the result of a National Cancer Institute [NCI] Workshop attended by 23 scientists. In that comprehensive review, under the Section entitled "Evaluating and validating noninvasive measurements of hypoxia," the authors state: "Consensus is . . . needed on an appropriate definition for hypoxia . . . **Methods shown experimentally to be linked with oxygen and hypoxia and with clinical outcome data - such as carbonic anhydrase IX (CA IX) - may be the most useful.**" [Tatum et al., page 734, col. 2; emphasis added.]

Under the next section of Tatum et al., entitled "Clinical treatment settings in which measurement of hypoxia would be of most value in treatment management," the authors conclude:

> Clinical studies now focus on confirming hypoxia as a prognostic marker for cancer outcomes and treatment response. . . . In those cases where response to treatment is rapid, it is not necessary for hypoxic assays to measure the level of hypoxia; a qualitative answer is enough. **However, for assessments related to outcome, survival, and treatment response, some quantitative results are needed. Carbonic anhydrase IX (CA-IX), for example, has been useful in segregating patients by expected outcome, but it might also be useful to develop ways to further stratify patients based on intermediate outcomes**.

[Tatum et al., page 735; emphasis added.] In other words, because of CA IX's close association with tumor hypoxia, CA IX

is uniquely suited as and expected to be a generalized tumor marker of several types of poor prognosis, such as "outcome, survival, and treatment response." Applicants respectfully argue that The Cancer Imaging Program of the National Cancer Institute would not consider the use of MN/CA IX as a generalized biomarker of different types of poor prognosis if they thought that its expression was unpredictable.

Also, as summarized by Potter and Harris in 2004,

> In a series of studies in breast cancer, lung cancer, cervical cancer and head and neck cancer the expression of CAIX has been independent of other routinely assessed factors and associated with poor prognosis. Comparison has been made with other markers such as GLUT1 and pimonidazole, and overall/ **[sic] CAIX seems to be the most robust marker**.

[Potter and Harris, Cell Cycle, 3(2): 164-167 (2004); at page 165, col. 2; emphasis added.] Those studies referred to by Potter and Harris include findings that MN/CA IX expression correlated with poor overall survival and outcome after radiation therapy in carcinoma of the cervix [Loncaster et al., Cancer Res., 61: 6394-6399 (2001)]; higher relapse rate and worse overall survival in invasive breast carcinoma [Chia et al., J Clin. Oncol., 19: 3660-3668 (2001)]; poor outcome in nonsmall cell lung cancer [Giatromanolaki et al., Cancer Res., 61: 7992-7998 (2001)]; poor survival in nasopharyngeal carcinoma [Hui et al., Clin Cancer Res., 8: 2595-2604 (2002)]; resistance

of squamous cell head and neck cancer to chemoradiotherapy [Koukourakis et al., Clin. Cancer Res., 7: 3399-3403 (2001)]; and poor survival in nonsmall cell lung cancer [Swinson et al., J Clin Oncol, 21: 473-482 (2003)].

More recent studies continue to support the association of CA IX with every type of poor prognosis. The one exception to the rule of CA IX association with poor prognosis in such tissues, in which CA IX is not normally expressed, that is, unlike the tissues that are the subject of the instant claims, has been renal cell carcinoma, which is the one disease identified in which CA IX induction by hypoxia has been uncoupled by a genetic mutation in the VHL gene. Therefore, Applicants respectfully submit that for the diseases of tissues in which CA IX is not normally expressed, contrary to the Examiner's statements in the Advisory Action, the use of MN/CA IX as a marker for different types of poor prognosis is predictable. One of skill in the art would predict that for any preneoplastic/neoplastic disease of tissues which do not normally express MN/CA IX, other than renal cell carcinoma, higher MN/CA IX expression would indicate poorer prognosis. To reiterate the standard for predictability set in MPEP § 2164.03, "If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art."

In the instant case, the Specification provides a pattern for cancer prognosis in tissues in which MN/CA IX is normally expressed, using gastric cancer as a working example. Applicants further respectfully argue as in their Amendments dated August 16, 2007, and December 19, 2007, that once a pattern of prognosis for a genus of diseases is established, it is conventional knowledge to apply those patterns for those diseases, in the absence of evidence to the contrary.

The Examiner concedes in the Advisory Action that the Specification is enabled for prognostic methods for a patient with gastric cancer, comprising determining that "said patient has a prognosis of shorter survival than the average subject with gastric cancer . . .". However, the Examiner indicates that "Tockman et al and Pastrokevo [sic] and Zavada provide evidence why one would not predict a single pattern of prognosis for the genus of diseases encompassed by the claimed methods." [Advisory Action, middle of page 3.] Applicants respond as above, that MN/CA IX has been shown to be such a reliable biomarker of poor prognosis in the unclaimed genus of diseases, that it is being considered by The Cancer Imaging Program of the National Cancer Institute as a generalized marker of poor prognosis related to hypoxia.

With respect to the lack of working examples for diseases other than gastric cancer, Applicants point out that

"[a]n example may be 'working' or 'prophetic.'. . . A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." [MPEP § 2164.02.] Although not strictly providing a "prophetic example," the instant Specification teaches [at page 42, lines 11-27] that renewed expression of MN/CA IX in tumor cells could signify hypoxia or tumor progression and corresponding poorer prognosis in diseases similar to gastric cancer. In the absence of any evidence to the contrary, Applicants respectfully conclude that ones of skill in the art would expect MN/CA IX's expression patterns in preneoplastic/neoplastic diseases are likely to apply to a broad range of tissues with analogous normal MN/CA IX expression patterns. That expectation is even stronger for the subject claims as amended for particularity and clarity to specify the tissues that are subject to the claimed methods.

Enablement Conclusion

Applicants respectfully point out that the link between high MN/CA IX expression and poor prognosis has been established in general for tissues in which MN/CA IX is normally not expressed. The instant invention addresses the other type of tissues, those in which MN/CA IX is normally expressed. A pattern for MN/CA IX and prognosis has been determined in the

first set of tissues, as indicated by the above quotes from Tatum et al. 2006 and Potter and Harris 2003. Once the instant application has provided evidence of the relationship between MN/CA IX expression and prognosis in the second set of tissues specifically set forth in the instant claims, there is no reason to doubt any variation from that pattern.

Applicants respectfully conclude that patent case law, as well as the MPEP, makes it clear that statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added.]

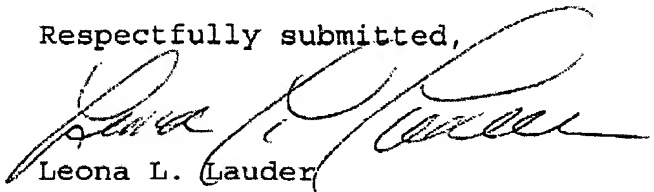
Applicants respectfully conclude that the Office has provided insufficient evidence of "reason to doubt" the objective truth of statements relied upon for enabling support in the Specification for the claimed invention. Further, Applicants have provided evidence and reasoning that counter any hypothetical burden of proof that could have been shifted to them by the citation of Tockman et al.

Applicants finally respectfully conclude that there can be no doubt that the scope of enablement provided in the subject application bears at the very least a "reasonable correlation" to the scope of the pending claims, particularly in view of the above claim amendments (discussed at length above). Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 USC § 112, first paragraph enablement rejection in view of the above remarks and explanations, patent case law discussion, clarifying claim amendments, and evidence presented.

CONCLUSION

Applicants respectfully conclude that the pending claims as amended are in condition for allowance, and earnestly request that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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